Cancer Chemother Pharmacol (2009) 63:525–528
DOI 10.1007/s00280-008-0778-7

ORIGINAL ARTICLE

Effect of antacid on imatinib absorption

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Received: 2 April 2008 / Accepted: 12 May 2008 / Published online: 24 May 2008

Abstract
Purpose Imatinib often causes gastric upset resulting in frequent co-administration of an antacid. Elevated gastric pH, delayed gastric emptying, or introduction of Mg^{2+}/Al^{3+} could potentially change imatinib absorption, thereby affecting the therapeutic effectiveness of imatinib. Indeed, antacid co-administration with dasatinib does result in a twofold decrease in dasatinib absorption. We aimed to define the effect of antacid on the pharmacokinetics of imatinib.
Methods Twelve healthy subjects were enrolled in a 2-period, open-label, randomized cross-over, fixed-sequence study. In one period, each subject received 400 mg imatinib p.o., and in the other, the same dose of imatinib preceded by 20 mL antacid, containing 1.6 g $Al(OH)_3$ + 1.6 g $Mg(OH)_2$, 15 min before imatinib. Plasma concentrations of imatinib and its active N-desmethyl metabolite CGP74588 were determined by LC–MS, and data were analyzed non-compartmentally.
Results Antacid administration did not significantly affect the area under the plasma imatinib concentration versus time curve (AUC) [31.7 μg/(mL h) alone versus 32.6 μg/(mL h) with antacid, $P = 0.37$; 80% power].
Conclusions Our results indicate that the use of Mg^{2+}-Al^{3+}-based antacid does not significantly affect imatinib absorption.

Keywords Imatinib · CML · GIST · Interaction

WinNonlin software was provided as part of the Pharsight Academic Licensing Program.

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Introduction

Imatinib mesylate (Gleevec®, Glivec®), a potent inhibitor of Bcr-Abl and c-Kit tyrosine kinases, is widely used to treat Philadelphia chromosome-positive leukemias and gastrointestinal stromal tumors [4–6]. Imatinib is associated with dyspepsia (18%) and nausea (43%) [6] and is therefore frequently administered with an acid-neutralizing antacid. Antacids increase the pH of the stomach content, delay gastric emptying, and introduce Mg^{2+} and Al^{3+} into the gastrointestinal tract. Each of these perturbations could theoretically decrease imatinib absorption, which normally exceeds 97%. Indeed, antacids are known to be associated

with a nearly twofold decrease in dasatinib absorption [1]. Whether, and to what extent, antacids used for imatinib-associated gastrointestinal upset influence imatinib pharmacokinetics is unknown.

The purpose of this study was to examine the effect of antacids containing magnesium and aluminum hydroxide salts on the pharmacokinetics of imatinib in healthy volunteers.

Materials and methods

Subjects

The study was approved by the University of Pittsburgh Institutional Review Board. After providing written informed consent, 12 healthy subjects (6 men, 6 women; 20–51 years) completed the study. Eligible subjects were healthy men or women who were 18 years of age or older and had a body mass index (BMI) <31 kg/m^2. Exclusion criteria included: pregnancy or breast-feeding; abnormal marrow function; evidence of renal dysfunction (proteinuria, estimated creatinine clearance <80 mL/min); impaired hepatic function (liver enzymes or bilirubin > the upper limit of normal); use of any medications (including over the counter products, herbal products, or mineral supplements) with the exception of a daily multivitamin preparation or oral contraceptives (for women).

Study design

The study had a 2-period, open-label, randomized cross-over, fixed-sequence design, and could detect a 30% difference in imatinib AUC with 80% power and a 5% type I error, assuming a within-subject variability of 30% [2]. In one period, subjects received 400 mg imatinib (Gleevec; Novartis Pharmaceuticals Corp, East Hanover, NJ) p.o., and in the other, 20 mL Maximum Strength Maalox®Max® Antacid/Anti-gas (Novartis) [1.6 g $Al(OH)_3$, 1.6 g $Mg(OH)_2$, 160 mg simethicone] was administered 15 min prior to 400 mg imatinib p.o. Imatinib was taken with 200 mL of water. The imatinib doses were separated by a wash-out period of 14 days in 11 patients and 21 days in 1 male patient.

Imatinib pharmacokinetics

Venous blood samples (N = 13 per subject, 6 mL each) were drawn from an indwelling catheter into heparin-containing tubes before and at 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, and 72 h after imatinib administration. Blood samples were centrifuged at 3,000 × g for 10 min, and the resulting plasma was aspirated and stored at −20°C or colder until analyzed.

Analytical procedures

Plasma concentrations of imatinib and its active N-desmethyl metabolite CGP74588 were determined using a previously described LC–MS method [7] that was developed and validated in our laboratory, after adaptation for use with a new instrument. Briefly, 0.2 mL plasma samples were mixed in a micro-centrifuge tube with 10 µL internal standard solution (5 µg/mL imatinib-D_8; Novartis) before plasma proteins were precipitated with 1 mL of acetonitrile. Samples were centrifuged for 5 min at 16,000 × g at room temperature, and the resulting supernatants were evaporated to dryness under a gentle stream of nitrogen at 37°C. Each dried residue was dissolved in 100 µL methanol:distilled water (30:70, v/v), transferred to an autosampler vial, and 3 µL were injected into the HPLC system. The HPLC system consisted of an Agilent model 1100 autosampler and quaternary pump (Agilent Technologies, Palo Alto, CA) and a Phenomenex Luna C18(2) (5 µm, 150 × 2 mm) reverse-phase analytical column (Phenomenex, Torrance, CA). Determination of imatinib, CGP74588, and the internal standard was achieved using a ThermoFinnigan MSQ Mass Spectrometer (Thermo Electron, San Jose, CA) operating in positive electrospray, single-ion mode monitoring m/z 493.7 for imatinib, m/z 479.7 for CGP74588 and m/z 501.7 for imatinib-D_8. Standard curves were linear over the range of 10–1,000 ng/mL, and exhibited acceptable performance (imatinib: accuracy −13.1 to 9.8% and precision within 6.8% CV; CGP74588: accuracy −5.3 to 6.7% and precision within 15.0% CV).

Pharmacokinetic analysis

The pharmacokinetic parameters of imatinib and CGP74588 were determined by standard non-compartmental methods (WinNonlin Professional 4.1, Pharsight, Mountain View, CA). The maximum concentration (C_{max}) and time to reach the maximum concentration (t_{max}) were determined by visual inspection of the plasma concentration versus time curves. The imatinib elimination rate constant (k_e) was obtained using non-linear least-square regression of the terminal concentration versus time data. The imatinib area under the concentration versus time curve (AUC) was calculated by the trapezoidal rule (linear up, log down) with extrapolation to infinity ($AUC_{0-\infty}$) beyond the last sample time (C_{last}). The percentage of $AUC_{0-\infty}$ extrapolated beyond C_{last} indicates what fraction of the $AUC_{0-\infty}$ is not based on our plasma determinations, but is estimated by extrapolation. Ideally the percentage extrapolated is less than 20%.

Statistical analysis

Calculations were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL). The pharmacokinetic parameter

estimates of imatinib and CGP74588 determined in the presence and absence of antacid were compared (after logarithmic transformation) with a two-tailed, paired *t* test, where a $P < 0.05$ was considered significant. We also tested for a sequence effect, to determine if there was a difference between the pharmacokinetics during the first and second study visit, unrelated to antacid co-administration. The values for imatinib t_{max}, CGP74588 t_{max}, and CGP74588 half-life, after log transformation, did not follow a normal distribution (significance observed by the Kolmogorov–Smirnov test for normality). Therefore, the untransformed values for these parameters were analyzed by the two-tailed exact Wilcoxon signed rank test.

We also performed an analysis of bioequivalence by calculating the 90% confidence intervals of the imatinib AUC ratio and the C_{max} ratio, based on log-transformed data, both of which should fall within the equivalence limits of 80–125% [3].

Results

Imatinib was well-tolerated by all 12 subjects, each of whom completed the study successfully. There was no sequence effect, i.e. the pharmacokinetics was not different between the first and second administration of imatinib. The pharmacokinetic parameter estimates for imatinib are shown in Table 1. The percentage of the AUC extrapolated beyond C_{last} was <5% for imatinib, allowing us to interpret our data with confidence. Concentration versus time curves of imatinib and CGP74588 in the presence and absence of antacid, respectively, are shown in Fig. 1.

The primary pharmacokinetic parameter to which this study was powered was imatinib AUC, a measure of the amount of imatinib absorbed. There was no significant difference in imatinib plasma AUC after dosing imatinib alone, compared to in the presence of antacid ($P = 0.37$). The 90% confidence intervals of the imatinib AUC ratio (mean 1.04, 90% confidence interval 0.96–1.12) and the C_{max} ratio (mean 1.00, 90% confidence interval 0.92–1.08), both fall well within the limits set for bioequivalence [3].

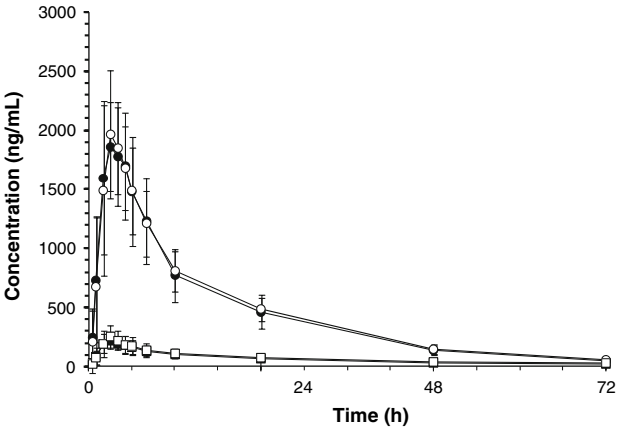

Fig. 1 Mean (± standard deviation) concentration versus time profile of imatinib (*circles*) and CGP74588 (*squares*) after administration of 400 mg imatinib without antacid (*solid*) and with antacid (*open*) to twelve healthy volunteers

We also examined the effect of antacids on other pharmacokinetic parameters for imatinib and CGP74588 (Table 1). We only detected a small difference in the AUC and clearance of CGP74588 (approximately 10%; $P = 0.03$).

Discussion

In conclusion, this study demonstrates that concomitant administration of a Mg^{2+}-Al^{3+}-based antacid is not associated with meaningful alterations in imatinib absorption. This is in striking contrast to dasatinib, where antacids have been associated with a nearly twofold decrease in dasatinib absorption [1]. The reason for this interaction is not clear, but may be due to limited dissolution of the dasatinib base in an environment with elevated pH, or due to chelation of the abundant Mg^{2+} or Al^{3+} cations by dasatinib, resulting in unabsorbable complexes. The small difference in the AUC

Table 1 Mean pharmacokinetic parameter estimates for imatinib and N-desmethyl-imatinib (CGP74588) alone and with co-administration of antacid ($N = 12$)

Analyte	Arm	AUC_{0-inf} (μg/mL h)	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)	V/F (L)	Cl/F (L/h)
Imatinib	Alone + antacid	31.7 (7.8)	2.06 (0.46)	2.8 (0.9)	14.6 (1.8)	281 (77)	13.4 (3.6)
		32.6 (6.0)	2.06 (0.48)	3.3 (0.7)	15.1 (1.8)	277 (72)	12.8 (3.1)
P value		0.37	1.00	0.17	0.25	0.90	0.37
CGP74588	Alone + antacid	5.78 (1.57)	0.26 (0.06)	2.6 (0.9)	30.5 (5.3)	3260 (1047)	74.1 (20.3)
		6.37 (1.75)	0.26 (0.09)	3.1 (0.5)	33.1 (9.2)	3217 (1175)	67.3 (18.2)
P value		0.025	0.75	0.27	0.37	0.66	0.025

The data are expressed as mean (standard deviation)

The percentage of the $AUC_{0-\infty}$ extrapolated beyond C_{last} was <5% for imatinib and <35% for CGP74588

and clearance of CGP74588 would not be expected to have any clinical relevance.

Acknowledgments We thank the nursing staff of the University of Pittsburgh Clinical Translational Research Center for their invaluable assistance, and the University of Pittsburgh Cancer Institute Hematology/Oncology Writing Group for constructive suggestions regarding the manuscript. This work was supported by Novartis Pharmaceuticals Corporation (East Hanover, NJ), and NIH/NCRR/CTSA Grant UL1 RR024153. WinNonlin software was provided as part of the Pharsight Academic Licensing Program.

References

1. Bristol-Myers Squibb Company (2007) Prescribing Information Sprycel(R) (dasatinib)
2. Cohen MH, Williams G, Johnson JR, Duan J, Gobburu J, Rahman A, Benson K, Leighton J, Kim SK, Wood R, Rothmann M, Chen G, KM U, Staten AM, Pazdur R (2002) Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. Clin Cancer Res 8:935–942
3. de Campos DR, Vieira NR, Bernasconi G, Barros FA, Meurer EC, Marchioretto MA, Coelho EC, Calafatti SA, Sommer C, Couto JM, Buranello S, Silva AR, Amarante AR, Abib E, Junior JP (2007) Bioequivalence of two enteric coated formulations of pantoprazole in healthy volunteers under fasting and fed conditions. Arzneimittelforschung 57:309–314
4. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CDM, Joensuu H (2002) Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 347:472–480
5. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, Capdeville R, Talpaz M (2001) Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 344:1038–1042
6. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, Sawyers CL (2001) Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 344:1031–1037
7. Parise RA, Ramanathan RK, Hayes MJ, Egorin MJ (2003) Liquid chromatographic-mass spectrometric assay for quantitation of imatinib and its main metabolite (CGP 74588) in plasma. J Chromatogr B Analyt Technol Biomed Life Sci 791:39–44